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EXAMINER

DEJONG, ERIC S

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1631

DATE MAILED: 09/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

10/088,269

Applicant(s)

KALLIONIEMI ET AL.

Examiner

Eric S. DeJong

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 18 July 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-5, 7-40 and 64-68 is/are pending in the application.
- 4a) Of the above claim(s) 15-40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5, 7-14, and 64-68 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)                                    | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED OFFICE ACTION**

### ***Interview Summary***

The interview summary provided by applicants in the response mailed 18 July 2005 is not found to be complete and accurate by the Examiner. See the MPEP § 713.04. Specifically, on page 9, third paragraph in applicants response, it is stated that "(a)greement was reached regarding various issues." To clarify this statement, the examiner points out, as cited in the Examiner Interview Summary, mailed 15 July 2005, that no agreement with respect to the allowability of claims was reached during the interview.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-14 and 64-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is newly applied and necessitated by amendment.

Claims 1, 64, and 68 each have been amended to recite the limitation "distinguishing spatially overlapping nucleic acid probe signals in the biological specimen" in lines 3-5 of instant claim 1, line 5 of instant claim 64, and lines 5 and 6 of instant claim 68. Upon review of the instant specification, no written description has been found to provide a basis for the above cited amendments to the instant claims. It is acknowledged that the specification provides for determining a three-dimensional relationship between signals that are vertically overlying, transversely overlapping, or non-contiguous signal, wherein the device used includes a confocal microscope. See for example, page 5, lines 1-15 of the instant specification. However, the above cited claim limitation is more broadly drawn to distinguishing spatially overlapping nucleic acid probe signals which does not require the use of a confocal microscope. As such, the above described amendment to the instant claims represents New Matter.

### ***Claim Rejections - 35 USC § 102***

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 10, 11, 13, 14, and 64 are rejected under 35 U.S.C. 102(e)(2) as being anticipated by Garini et al. (U.S. Patent No. 5,817,462). This rejection is necessitated by amendments to the instant claims.

The instant claims are drawn to a computer implemented method for counting nucleic acid probe signals in a multi-cell region of interest in a biological spectrum

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comprising, obtaining a plurality of successive images of the region, distinguishing spatially overlapping nucleic acid probe signals, automatically counting a number of test signals from a test probe, automatically counting a number of reference probe signals, and determining a ratio of the automatically-counted test signals to the automatically counted reference signals.

Claims 1, 64, and 68: Garini et al. discloses a spectral imaging method and computer related systems for simultaneous detection of multiple fluorophores aimed at detecting and analyzing in situ hybridizations employing numerous chromosome paints and loci specific probes (a method for counting nucleic acid probe signals in a region of interest in a biological specimen). See Garini et al., Abstract. The spectral algorithms, processing and visualization techniques are specifically directed toward computer implemented applications and read on the claimed computer-implemented method and computer systems. See Garini et al, at least column 16, lines 38-56 and column 19, line 9 through column 20, line 61. The disclosed method provides for the analysis of multiple cell (defined as " both a biological cell and also a region in the field of view of the instrument") types stained with different fluorophores, wherein an algorithm is applied to analyze a given cell or region for each type of fluorescent signal being used and provide a count of the number of cells or regions pertaining to each fluorophore (in a computer system, automatically counting a number of test signals from a test probe; in a computer system, automatically counting a number of reference signals from a reference probe; the region of interest comprises multiple cells). See Garini et al., column 19, line 9-48 and column 27, line 33-59. It is further emphasized in Garini et al., column 54, lines 28-

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40, that the algorithms disclosed and incorporated into the method employ automatic procedures that are well known in the art. Further, Garini et al. discloses the determination of a ratio between multiple frequencies of fluorescence pertaining to different probes hybridized to chromosomes or specific loci (determining a ratio of the automatically-counted test signal from the test probe to the automatically-counted reference signals from the reference probe). See Garini et al., column 9, line 26-35 and column 23, line 18 through column 24, line 8. Garini et al. teaches sequentially acquiring images of the emissions of multiple fluorescent probes to address the issue of overlapping signal in probe samples (obtaining a plurality of successive images of the region of interest to distinguish signals in the biological specimen). See Garini et al., column 16, lines 19-63 and column 23, lines 7-27.

Claim 2: Garini et al. discloses the use of centromere specific DNA probes in Example 1, column 37, line 66 through column 38, line 27 (the reference probe is a polynucleotide that hybridizes to a centromere). Further Garini et al. discloses an embodiment of the invention wherein probe hybridization is directed to chromosomal loci and provides for the detection of a cell nucleus. See Garini et al., column 6, line 66 through column 67, line 42. Example 1 also teaches that duration of exposing a sample to hybridizing probes directly relates to the amount of observable probes signal, and therefore, under a broad interpretation, each measurement of probe signal provides for an approximation of the probe target present in a given sample rather than an absolute measurement of all possible probe targets (the number of reference signals from the reference probe approximates a nucleus count in the biological specimen).

Claim 3: Garini et al. discloses that a fluorescent in situ hybridization method available to the disclosed invention can provide information on the location of the labeled probe, the number of labeled sites on each chromosome, and the intensity of labeling at each site (the reference probe recognizes a target on a same chromosome as the test probe). See Garini et al., column 26, lines 45-58.

Claims 4 and 5: Garini et al. discloses the invention can be used to analyze genes at the chromosome level (the test probe is a polynucleotide that hybridizes to a target sequence in a gene, and the reference probe is a polynucleotide that hybridizes to a reference sequence). See Garini et al., column 25, lines 16-23. Further, it is disclosed that this is an important example of where “the detection of multiple fluorescent probes can be a significant advantage” (the reference probe recognizes the same chromosome on which the gene of interest is contained). See Garini et al., column 25, lines 16 and 17.

Claims 10 and 11: Garini et al. teaches that the imaging spectrometers used in context of the disclosed invention measure the intensity of light coming from every pixel in the field of view, but also measure the spectrum of each pixel in a predefined wavelength range (a quantity of the test probe signals and reference probe signals are determined). See Garini et al., column 3, lines 46-59 and column 15, lines 44-58.

Claims 13 and 14: Garini et al. provide pictures obtained using the disclosed invention wherein multiple fluorescent probes were hybridized to chromosomes and establish a standard karyotype display without any reference to the boundaries of a cell nucleus or a cell (the ratio of signals is determined without reference to boundaries of a

cell nucleus, without reference to the boundaries of a cell). See Garini et al., for example Figures 9A, 9B, 10 and 11.

### ***Response to Arguments***

Applicant's arguments filed 18 July 2005 have been fully considered but they are not persuasive.

Applicants have amended claim 1 to recite the limitation "obtaining a plurality of successive images of the region of interest; with the plurality of successive images of the region of interest, distinguishing spatially overlapping nucleic acid probe signals in the biological specimen" in lines 2-5 of the instant claim. Further, applicants argue that Garini et al. anticipate the limitation of "distinguishing spatially overlapping nucleic acid probe signals" on page 10, lines 29-30 of applicants response.

Garini et al. characterizes the disclosed methods and systems as pertaining to a spectral image analysis as a three-dimensional technique that extracts features, including resolving spatial features, from a combination of spectral information with spatial organization. Garini et al., column 16, lines 19-26 states:

"As mentioned above, a spectral image is a three dimensional array of data,  $U(x,y,\lambda)$ , that combines spectral information with spatial organization of the image. As such, a spectral image is a set of data called a spectral cube, due to its dimensionality, which enables the extraction of features and the evaluation of quantities that are difficult, and in some cases even impossible, to obtain otherwise."

Thus, the method disclosed by Garini et al. distinguishes overlapping probe signals by selecting different frequencies present in a given three-dimensional array of data,  $U(x,y,\lambda)$ , wherein spatially overlapping signal from multiple probes may be resolved by

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selecting for particular probe frequency and allowing signal of one probe to be distinguished over signal from adjacent probes. Garini et al. further contrasts this technique with a more traditional 3D(x,y,z) analysis resolving spatially overlapping probe signal. See Garini et al., column 17, lines 1-54. Since the instant claims do not recite any limitation requiring that overlapping probe signals emit at the same spectral frequency, the method of resolving fluorescent overlapping signals disclosed by Garini et al., therefore, anticipates the instant claim.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 7-14 and 64-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garini et al. in view of Cabib et al. (U.S. Patent No. 5,784,162). This rejection is necessitated by amendments to the instant claims.

The instant claims are drawn to a computer implemented method for counting nucleic acid probe signals in a multi-cell region of interest in a biological spectrum comprising, obtaining a plurality of successive images of the region, distinguishing spatially overlapping nucleic acid probe signals, automatically counting a number of test signals from a test probe, automatically counting a number of reference probe signals, and determining a ratio of the automatically-counted test signals to the automatically counted reference signals.

Garini et al., as discussed above, discloses a spectral imaging method, system and means for simultaneous detection of multiple fluorophores aimed at detecting and analyzing in situ hybridizations employing numerous chromosome paints and loci specific probes. However Garini et al. does not fairly teach the claimed invention wherein successive images are optical sections of the region of interest, are at different depths of the biological specimen, are transformed into digital representations in which contiguous signal segments are combined into a single signal, or are obtained by confocal microscopy.

Garini et al. does teach that the disclosed invention is potentially useful in all applications in which spectral differences exist between chemical constituents whose special distribution and organization within an image are of interest, and that the spectral imaging methods disclosed in Cabib et al. (U.S. Patent No. 5,784,162) can be

used to detect such spatial organization in a given sample. See Garini et al., column 5, lines 16-47.

Claims 7, 8, 65, and 66: Cabib et al. disclosed a mapping technique in the context of the disclosed invention that allows for image acquisition by focusing on specific depths within a cell (successive images are optical sections; the optical sections are at different depths of the biological specimen). See Cabib et al., column 38, line 47 through column 39, line 9.

Claims 9 and 67: The instant limitation of successive images being transformed into digital representations in which contiguous signal segments in successive optical scans are combined into a single signal in a particular optical section, under a reasonably broad interpretation, can be read as simply a two-dimensional digital representation of contiguous optical layers. Figure 12 and the related caption found in Cabib et al., column 14, lines 14-31, reads on the broad interpretation instant limitation, as images of multiple levels of fluorescence images taken of a paramecium are presented as well as an overall (combined) fluorescence image of the paramecium. Further, Cabib et al. establish that the disclosed invention embodies images derived from both spectroscopic and digital methods that are well known in the art. See Cabib et al., column 19, lines 28-41.

Claims 12: Cabib et al. specifically disclose that preferred embodiments the microscope is selected from the group consisting of a reflection microscope, a transmission microscope, a fluorescence microscope, an upright microscope, an inverted microscope, a dark field microscope, a confocal microscope, a standing wave

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confocal microscope and a reflection contrast microscope (wherein successive images are obtained by confocal microscopy). See Cabib et al., column 7, lines 53-59.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ the spectral imaging method, system and means for simultaneous detection of multiple fluorophores aimed at detecting and analyzing in situ hybridizations employing numerous chromosome paints and loci specific probes as taught by Garini et al., wherein successive images are optical sections of the region of interest, are at different depths of the biological specimen, are transformed into digital representations in which contiguous signal segments are combined into a single signal, or are obtained by confocal microscopy, because Garini et al. teaches that the disclosed invention is potentially useful in all applications in which spectral differences exist between chemical constituents whose special distribution and organization within an image are of interest.

### ***Response to Arguments***

Applicant's arguments filed 18 July 2005 have been fully considered but they are not persuasive.

Applicants argue that Garini et al. and the Cabib et al. discussion of "specific depths of the cell" fails to teach or suggest the recited "distinguishing overlapping probe signals" as instantly claimed. See page 12, lines 3-6. Further, applicants point out that Cabib et al. is incorporated by reference into the disclosure of Garini et al., that such incorporation by reference does not provide sufficient motivation to combine, and

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neither of the applied references provides any sufficient motivation to combine. See page 13, lines 31-33.

Applicants arguments are not directed to the basis of the rejection regarding instantly claimed limitation drawn to distinguishing overlapping probe signals. For the reasons provided above, the limitation of "distinguishing spatially overlapping probe signals" is anticipated by Garini et al. Therefore the argument that the Cabib et al. discussion of "specific depths of the cell" fails to teach or suggest the recited "distinguishing overlapping probe signals" as instantly claimed is not germane to the instant rejection.

The Examiner points out that applicants arguments regarding the motivation to combine the references of Garini et al. and Cabib et al. is not directed to the merits of the previously presented rejection. The previous rejection did not rely on the incorporation of Cabib et al. into the disclosure of Garini et al. as the source for motivation to combine, but rather provided the reference to Cabib et al. Garini et al. as exemplifying the Garini et al. teaching that the disclosed invention is potentially useful in all applications in which spectral differences exist between chemical constituents whose special distribution and organization within an image are of interest. Further, on page 13, lines 32 and 33, applicants state "Applicants cannot find within either the references sufficient motivation to combine or modify that would result in the claimed arrangement". Again, applicants statement does not address the motivation to combine which was provided and reiterated from the previous office action. See the previous Office action, page 7, lines 9-14 and page 8, lines 15-22.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center at (800) 786-9199.

EDJ

*John S. Brusca 20 September 2005*  
JOHN S. BRUSCA, PH.D  
PRIMARY EXAMINER